INTRACELLULAR FATE OF FGFRs WITH BIOAMBIENTS

Maria Grazia Vigliotti **Steffen van Bakel** **John. K. Heath**

Abstract. Reactions in signaling pathways can vary according to the location of components. A typical example of this kind of pathway is the receptor-mediated endocytotic pathway. To faithfully model these pathways, there is a need to explicitly represent different compartments of the cell to finely describe the relocation of components. In our work, we consider a spatial model for different sorting of receptors of Fibroblast Growth Factor via the endocytotic pathway.
As computational model, we use the stochastic version of BioAmbients, a process calculus that allows to model both signaling pathways and the spatial distributions of signaling. The stochastic simulation is carried out using BAM (BioAmbient Machine), a Java implementation of BioAmbients via a spatial version of the Gillespie Algorithm. Our model, and the associated results of the simulations, confirm known experimental data. Our work [4] sheds light on different mechanisms that influence the spatial distribution of the different components in the pathway.

Process Algebras in System Biology - Process algebra are a formal tool used for **specification** and **analysis** of concurrent systems. The key ideas [2] for modeling in System Biology is to encode the interaction-capabilities of every molecule in a process-algebraic term, to put all terms together, and use the native semantics of the language to simulate the behaviour of the system.

Molecules	Processes
Interaction	Communication
Locations	Compartments

FGFR MODEL IN BIOAMBIENTS

LYSOSOME = [L | . . . | L]
ENDOSOME = [EN | . . . | EN]
LATENDOSOME = [LE | . . . | LE]
RECYCLE = [R | . . . | R]

} Compartment / Locations

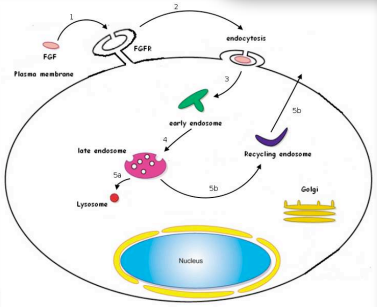
L = accept lyso.L
EN = accept endo1.EN + expel endo2.EN
LE = accept lendo1.LE + expel lendo2.LE
R = accept recycle1.R + expel recycle2.R
C = p2c fgfbind(x).enter endo1.exit endo2.enter lendo1.C1
C1 = exit lendo2.(enter lyso.S + enter recycle1.exit recycle2.C)
FGF = p2c fgfbind⟨bind⟩
FGFR = [C]

ALGORITHM

1. If FGF1 is outside the cell and FGFR_1 **...** FGFR_4 are located on the cell's surface, **then** FGF1-FGFR_i forms a compound;
2. A vacuole is formed and the FGF1-FGFR_i enter the cell;
3. The FGF1-FGFR_i complexes move to the early/sorting endosomal compartment;
4. From the early endosome, FGF1-FGFR_i complexes are routed to the late endosome.
5. From the late endosome:
(a) **if i=1,2,3 then** the FGF1-FGFR_i complex moves into lysosome; first FGF1-FGFR_i separate, then degrade.
(b) **if i=4 then** the FGF1-FGFR_i complex moves into the endosomal recycling compartment, and:
(i) FGF1-FGFR_4 separate;
(ii) FGF1 degrades;
(iii) FGFR_4 returns back to surface.

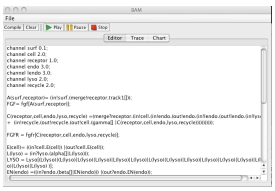
ADVANTAGES OF BIOAMBIENTS

BioAmbients present several advantages:
• **Abstraction**;
• **Compositionality** - the model can be built in parts, bottom-up;
• **Rigorous method** of describing interaction between agents;
• Direct translation into stochastic processes;
• Easy modifiable code;
• No complete recoding needed for small changes.



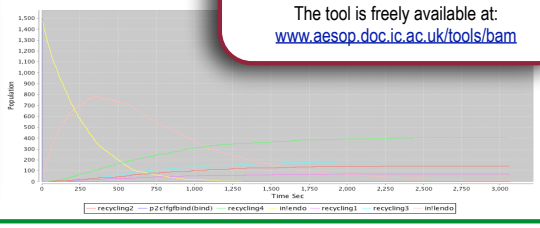
TOOL: BAM

BAM is a simulator for stochastic BioAmbients written in Java 1.5. The core functionality of the tool is to simulate, using Gillespie's algorithm, the behaviour of the Continuous Time Markov Chain that underlies the BioAmbients. The tool automatically produces both a simulation graph and a debugging trace of the program[5]



The tool is freely available at:
www.aesop.doc.ic.ac.uk/tools/bam

SIMULATION RESULTS



EXPERIMENTAL RESULTS

In [2], experiments were carried out to establish the fate of the ligand and receptor after binding. The results show that two different routes of movement exist within the cell, depending on which FGFR the FGF1 has bound with. FGF1 internalised by FGFR1-FGFR3 is generally routed to the lysosomes for degradation and FGF1 internalised by FGFR4 is mainly routed to the recycling compartment.

References:[1] A.Regev et.al. Bioambients: an abstraction for biological compartments. TCS, 325(1):141–167, 2004. [2] A.Regev and E.Y. Shapiro. Cellular abstractions: Cells as computation. Nature, 419(343), 2002. [3] E. M. Haugsten et.al. Different intracellular trafficking of fgf1 endocytosed by the four homologous FGF receptors. Journal of Cell Science, 118:3869–3881, 2005. [4] M.G Vigliotti et.al. Modeling the intracellular fate of FGF receptors in BioAmbients. QAPL'08, ENTCS 220,181-197, 2008 [5] V. A. Muganthan et.al. BAM: BioAmbient Machine. In Proc. of ACSD'08. IEEE Society, 2008.

mgv98@doc.ic.ac.uk, Department of Computing, Imperial College, 180 Queen's Gate, London, UK